SYNTHESIS OF SUBSTANCES EFFECTING C. N. S. VIII

Synthesis of New Diindolylmethane Derivatives Effecting C. N. S.

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Some derivatives and bis-Mannich bases of diindolylmethane have been prepared from indol with oxo-compounds and from indols substituted in 4-, 5- and 6-positions with formaldehyde. The mechanism of formation of diindolylmethane as well as that of the Mannich reaction has been studied by means of thin-layer chromatography.

The condensation reaction of indol with benzaldehyde and benzoylchloride was studied first by FISCHER [1, 2]. „Roseindol" formed from indol and benzoylchloride was reduced by zinc in glacial acetic acid to give the same compound as obtained by the reaction of benzaldehyde and indol. As to the structure of the compound thus formed he supposed that two indolyl radicals were coupled in the molecule by the benzylidene-radical. Indolidene indolyl-phenylmethane („roseindol"), as well as diindolyl-phenylmethane, formed from benzaldehyde and indol, can be transformed into each other by oxidation and reduction, respectively. The structure of products formed from indol with oxo-compounds has been studied in detail by FREUND and his coworkers [3], SCHOLTZ [4] and by other investigators [5, 6]. According to them indol and an oxo-compound in a mole ratio of 2:1 gives a diindolylmethane derivative, while in a mole ratio of 1:1, or in strong acidic media [7, 8] it produces indolidene (ketal) derivative. It has already been supposed by GOLDSCHMIDT [5] and HARRISS [6] that depending on the pH, indol takes part in the reactions in two tautomeric forms (indol—indolenin) what has lately been proved by formation of isonitrosoindol [9] and other reactions as well, and more recently by spectra of nuclear magnetic resonance (NMR) [10, 11]. The synthesis of diindolylmethane has been carried out by THESING in three ways:

a) from indol with formaldehyde solution in aqueous neutral media;

b) from 3-oxymethylindol in aqueous media at pH 5,5, and

c) from indol magnesium bromide with paraformaldehyde.

Its formation as a by-product has also been observed in the synthesis of gramine [13]. Recently the optimum pH for the formation of diindolylmethane has been studied by KAMAL and his coworkers [14] using different aldehydes and series of pH. This optimum pH value was found to be 2,5—3,5.

According to data given in the literature the formation of diindolylmethane takes place in two steps: from indol and formaldehyde 3-oxymethylindol is formed which gives 1,3-diindolylmethane with indol in a bimolecular substitution reaction. The mechanism of formation of diindolylmethane, as it is clear from our investigations, is not so simple, the process is much more complex. Our experiments carried out in this respect can be summarized as follows:

In a 2:1 mole reaction mixture of indol and formaldehyde the amount of products formed and their changes were followed by thin-layer chromatography. The intermediate products appearing in the chromatogram were isolated, their structure determined or in case of compounds which could hardly be identified the structures were deduced in some other ways. From changes in time of spots appearing in the chromatogram and from the results of experiments carried out with corresponding pairs of isolated compounds we concluded the reaction mechanism (see below).

The chromatogram of formation of diindolylmethane is to be seen in Fig. 1, showing spots of different products formed with the progress of the reaction. (0,002 mole indol, 0,001 mole 38% formaldehyde solution in 2 ml methanol of 60%; pH 3,5, 25 °C on a 0,25 mm Kieselgel G plate. Tempering agent: benzol: c-hexane: ethanol in a volume ratio of 5:4:1. Developed in iodine vapour.)

The intermediate products of the process with the exception of III and V could be isolated by changing the conditions of the reaction, thus their structure could also be determined. The following compounds correspond to the certain spots of the chromatogram:

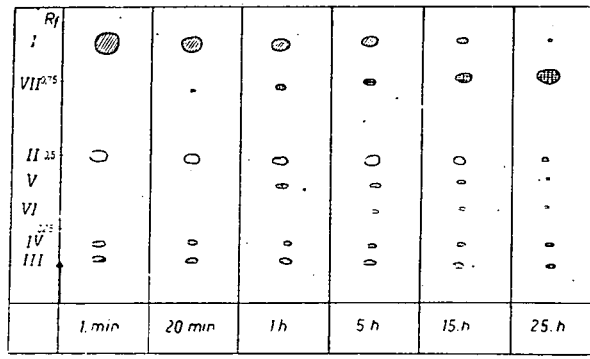


Fig. 1

I. indol

II. it is formed from indol on applying formaldehyde in excess, in strong alkaline media at room temperature. As testified by analysis and the infra-red spectra, it is N-oxymethyl indol.

III. (see note to Fig. 2).

IV. it could be identified with 3-oxymethylindol prepared from 3-indolaldehyde by catalytic hydrogenation [15].

V. it could not be isolated, however, is supposed to be N-oxymethyl-3,3′-diindolylmethane, since it is formed from diindolylmethane together with formaldehyde besides isolated N,N′-bisoxymethyl-3,3′-diindolylmethane.

VI. it is formed from diindolylmethane in alkaline and acidic media as well. On the basis of the analysis and infra-red data it proved to be N,N′-bisoxymethyl-3,3′-diindolylmethane.

VII. identified with 3,3′-diindolylmethane prepared from indol with formaldehyde.

In order to clear up the mechanism of the reaction besides the former investigations the reaction of the isolated intermediates with each other has also been studied and to follow up the transformation similarly the thin-layer chromatography was applied. The experiment, on the basis of the spots in the chromatogram can be evaluated as follows (Fig. 2). Tempering and developing as in Fig. 1.

Column 1. The reaction of indol and formaldehyde (2:1 mole ratio, pH 3,5) in two hours. Compounds II and VI are formed during the reaction.

Column 2. Compound II (under conditions similar to those in the reactions of Column 1) partly transformed into indol. It is to be noted that in dry media as e. g. chloroform, ethanol or benzol, II does not change even on heating, and fused over its melting point it does not decompose.

On the basis of the chromatogram, under the conditions of the reaction an equilibrium must be supposed between indol and N-oxymethylindol.

Column 3. Compound IV does not change allowed in dry alcohol for 2 hours.

Column 11. Under the given reaction conditions (pH 3,5) IV changes into VII, I and V in two hours. This can only be interpreted by supposing an equilibrium between 3-oxymethylindol and indol.

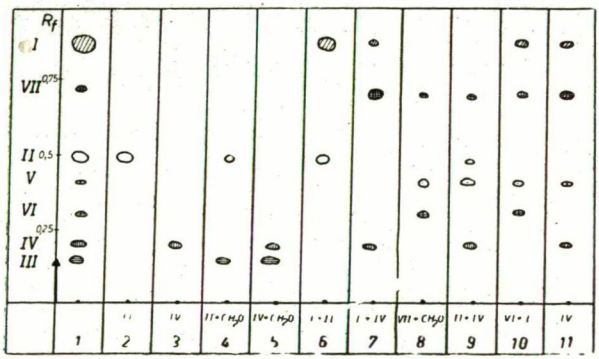


Fig. 2

Columns 4 and 5. With formaldehyde II and IV equally gives III. The latter is stable only in solution, in the isolating procedures it decomposes to IV. Since from N-oxymethylindol (II) and 3-oxymethylindol (IV) the same compound (III) is formed with formaldehyde, III can be supposed to be identic with N,3-bisoxymethylindol.

Column 6. Reaction between I and II does not take place, no new compound is formed and an equilibrium can be set in between the two.

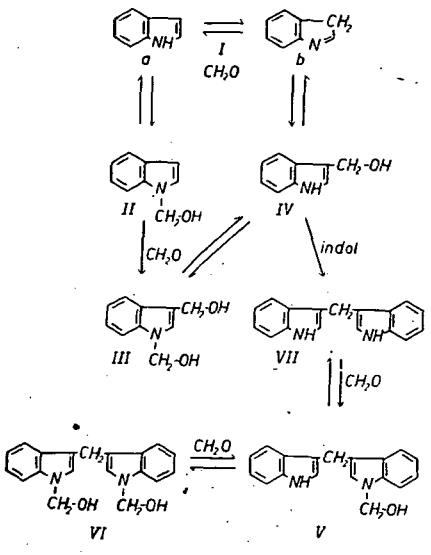


Fig. 3

Column 7. IV changes with I into diindolylethane (VII).

Column 8. Compound VII with formaldehyde changes into N-oxymethyl-diindolylmethane (V) and N,N'-bisoxy-methyl-diindolylmethane (VI).

Column 9. By reaction IV with II after a prolonged time, N-oximethyldi-indolylmethane (V) is formed.

Column 10. Compound VI with I gives partly diindolylmethane (VII).

Summarizing the results of chromatographic experiments the formation of diindolylmethane can be supposed to take place according to the scheme shown in Fig. 3.

Tautomeric (a, b) equilibrium, as shown by the extension of II and IV spots in the chromatogram (Fig. 1) under the given reaction conditions is shifted approximately in 70% toward A. From Ia N-oxymethylindol (II) and from Ib 3-oxymethylindol (IV) are formed. In the first period of the reaction, when VII is not yet formed, the ratio of the two compounds is about 3:1. N-oxymethylindol, formed in larger quantities (II), step-bystep changes through III into 3-oxymethylindol (IV), because the latter falls out from equilibrium III ⇌ IV owing to the formation of diindolylmethane.

Thus the reaction leads to diindolylmethane (VII) in two directions:

a) 3-oxymethylindol (IV) → diindolylmethane (VII), and

b) N-oxymethylindol (II) → N,3-bisoxymethylindol (III)
3-oxymethylindol (IV) → diindolylmethane.

Compounds V and VI are formed in small quantities from diindolylmethane in the reaction mixture with formaldehyde, thus it does not seem probable that V and VI would play a decisive role in the formation of diindolylmethane.

Indols substituted in 4-, 5- and 6-positions, used as starting substances, were prepared by the methods of JAPP—KLINGEMAN, REISSERT and THESING (Table I). The substituted diindolylmethane derivatives were obtained from these compounds with formaldehyde (Fig. 4). It is to be noted that the reaction takes also place with substituted indols according to the mechanism mentioned above.

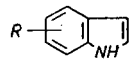
The MANNICH-type reaction of diindolylmethane has been studied and described by THESING [24]. He has also pointed out by spectroscopy, that the tertiary-aminomethyl group is coupled with nitrogen of the indol-skeleton. It is generally proved that 3-substituted indols take part in the MANNICH condensation with their-NH-groups.

According to our experimental observations the ratio of the MANNICH base-formed in the reaction to the side-products largely depends on the order of pour ing the reaction-components (diindolylmethane, formaldehyde, etc., sec. amine)

and this is in connection with the reaction mechanism. This problem, since there are no data on the mechanism of this reaction available in the literature, was also studied by us in detail.

The MANNICH reaction of diindolylmethane in aqueous alcohol, in the presence of potassium hydroxide takes place rapidly and quantitatively yields the MANNICH base. In acidic media (pH 4), however, the reaction does not take place at all. From this follows that the process occurs according to the mechanism of

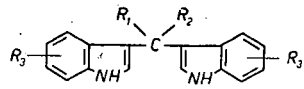
Table I



R	Summary form	M. w.	Mp.	Method	References	Basic Compound	Ref.
H	C_8H_7N	117,14	52,5	Fluka		—	—
5-Cl	C_8H_7NCl	152,61	71–72	a	[17]	p-klóranilin	[16]
6-Cl	C_8H_7NCl	152,61	78–80	b	[17],[18]	2-nitró-4-klór toluol	—
4-Br	C_8H_7NBr	197,07	olaj	b	[20],[21]	2-nitro-6-klór toluol	[19]
5-Br	C_8H_7NBr	197,07	90–91	a;c	[23],[28]	p-brómanilin	[16]
6-Br	C_8H_7NBr	197,07	94	b	[20],[21]	2-nitro-4-bróm toluol	[19]
5-J	C_8H_7NJ	244,06	99–100	c	[23]	indol	Fluka
6-CH_3	$C_9H_{10}N$	132,19	13,5–14	b	[22]	2-nitro,1,4-di-metilbenzol	[22]
5-NO_2	$C_8H_7N_2O_2$	163,16	140–141	c	[23]	indol	Fluka

Note: a) Japp-Klingemann method
b) Reissert method
c) Jan Thesing method

pip. = piperidine;
mor. = morpholine



R_1	R_2	R_3	Compound	R_1	R_2	R_3	Compound
H	H	H	VII.	H	H	5-Br	XIV
CH_3	CH_3	H	VIII.	H	H	6-Br	XV
H	CH_3	H	IX.	H	H	5-J	XVI
H	n-C_3H_7	H	X.	H	H	6-CH_3	XVII
H	H	5-Cl	XI.	H	H	5-NO_2	XVIII
H	H	6-Cl	XII.				
H	H	4-Br	XIII.				

Fig. 4.

base catalyzed MANNICH reaction (CUMMINGS [26]), instead of that of the carbenium-immonium ion, described by HELLMAN [25]. But the question had to be decided, whether N-oxymethyl-tertiary amine was first formed in the reaction, or N,N'-bisoxymethyl-diindolylmethane (VI). It is important, because under the conditions of the reaction (alkaline medium) the formation of both compounds seemed to be possible. The experiments done proved that N,N'-bisoxymethyl-diindolylmethane (VI) did not enter into reaction with sec. amine, therefore under such conditions MANNICH base was not formed. This experiment unequivocally proves that N-oxymethyl-tertiary amine is formed first in the reaction and this reacts with diindolylmethane. Having all the results the mechanism of the MANNICH reaction of diindolylmethane can be interpreted as shown in Fig. 5.

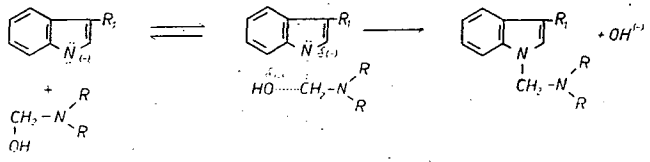


Fig. 5a

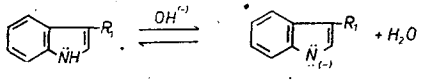
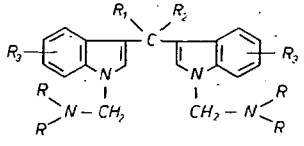


Fig. 5b

Hydroxyl ion playing the part of the catalyst detaches proton from the nitrogen of indol skeleton and this proton, as a nucleophilic center, enters into a bimolecular reaction with N-oxymethyl sec. amine (S_{N2}). In the light of this mechanism of the process it becomes clear that the reaction is dependent on the order of mixing the



R_1	R_2	R_3	R_2N-		R_1	R_2	R_3	R_2N-	
H	H	H	pip.	XIX	H	H	4-Br	pip.	XXVI
H	H	H	mor.	XX	H	H	5-Br	pip.	XXVII
CH_3	CH_3	H	pip.	XXI	H	H	6-Br	pip.	XXVIII
H	CH_3	H	pip.	XXII	H	H	5-J	pip.	XXIX
H	n-C_3H_5	H	pip.	XXIII	H	H	6-CH_3	pip.	XXX
H	H	5-Cl	pip.	XXIV	H	H	5-NO_2	pip.	XXXI
H	H	6-Cl	pip.	XXV					

Fig. 6.

components. Nanely, if first formaldehyde is added to diindolylmethane solution, N,N'-bisoximethyl-diindolylmethane is formed with a considerable rate and this cannot give MANNICH base with sec. amine. The very rapid occurring of the reaction is promoted by choosing the optimum ratio of the solvent mixture (ethanol-water), so that MANNICH base formed in the equilibrium should separate already during the reaction. (Under such conditions 20—30 g diindolylmethane changes quantitatively into MANNICH base in 10—15 min at 70—80 °C.)

MANNICH bases prepared from diindolylmethane derivatives with formaldehyde and sec. amine are illustrated in Fig. 6.

Experimental

N-oxymethylindol (II)

2,34 g indol (0,02 mole) was suspended in 15 ml of 40% potassium hydroxide solution, 8 ml of 38% formaldehyde (0,1 mole) was added and the suspension heated under constant stirring at 40 °C for 1—2 min, then stirring was continued at room temperature till indol completely changed into solution (15—20 min). After addition of 15 ml distilled water it was allowed to stand in a refrigerator In 10—12 hours N-oxymethyl-indol crystallized, was filtered, washed in distilled water until it became free of alkaline and recrystallized from benzene — petrolether.

M. p. 51—52 °.

Yield: 2,2 g (75%).

Anal.: Calcd. C_9H_8ON C 73,42 H 6,13 N 10,89 Found.: C 73,35 H 6,50 N 10,90

N,N'-bisoximethyl-3,3'-diindolylmethane (VI)

2,46 g of VII (0,01 mole) was dissolved in dry ethanol, 5 ml of 1% potassium hydroxide solution was added together with 2 ml of 38% formaldehyde (0,025 mole). It was refluxed in a waterbath, allowed to stand at room temperature. In 2—3 hours compound VI separated as needles from the solution. It was filtered and washed with ethanol.

M. p. 152 °.

Yield: 2,80 g (91,5%).

Anal.: Calcd. $C_{19}H_{15}O_2N_2$ C 74,49 H 5,99 N 9,14 Found: C 74,45 H 5,95 N 8,97

3-oxymethylindol (VI)

3,54 g of indol (0,03 mole) was suspended in 10 ml of 40% potassium hydroxide solution, added 3,20 ml of 38% formaldehyde (0,04 mole). The suspension was heated at 40 °C for 40 min while constant stirring. (Indol, first forming N-oximethyl-indol, dissolved, later the solution breaks, becomes like an emulsion.) Heating for more than 40 min or the appliaction of higher temperatures decreased the yield owing to by-reactions). After cooling the emulsion was extracted with ether, the etheric solution washed with water, dried over dry sodium sulphate and the solvent removed from a 25 °C water-bath at a low pressure. The residual crystalline mass was twice recrystallized from benzene.

M. p. 90—91 °.

Yield: 2 g (45%). The substance was identified with 3-oxymethylindol prepared from 3-indolaldehyde by hydrogenation.

Anal.: Calcd.: C_9H_8ON C 73,42 H 6,13 N 9,52 Found: C 73,30 H 9,20 N 9,62.

3,3'-diindolylmethane

According to [12] it had been prepared from indol with formaldehyde in aqueous medium. The yield was almost quantitative.

M. p. 168—9 °C. Recrystallized from propanol:

M. p.: 170 °.

1,1-bismorpholynomethyl-3,3'-diindolylmethane (XX)

2,46 g of VII (0,01 mole) was dissolved in 25 ml ethanol by heating and after complete dissolution 1,74 g of morpholine (0,02 mole) was added together with 1,6 ml of 38% formaldehyde (0,02 mole) and 2 drops of 5% potassium hydroxide solution. It was refluxed for 40 min in a water bath then allowed to stand at room temperature. After a few hours the crystallized products were filtered, washed with ethanol and recrystallized from ethanol-benzene mixture (3:1).

M. p. 183 °.

Yield: 3,8 g (84%).

Anal.: $C_{27}H_{32}O_2N_2$ Calcd.: C 72,93 H 7,26 N 12,61 Found C 72,82 H 7,42 N 12,85.

1,1'-bispiperidinomethyl-3,3'-diindolylmethane (XIX) [29]

2,46 g of VII (0,01 mole) and 1,70 g of piperidine (0,02 mole) were dissolved in 20 ml of ethanole. 1,60 ml of 38% formaldehyde (0,02 mole) and 0,3 ml of 5% potassium hydroxide solution were added to the solution and cooled to 30 °C. It was heated for 20 min in a water bath under refluxing, then 5 ml of distilled water was added to the solution. After cooling it quickly crystallized, was filtered and washed with ethanol.

M. p.: 140—141 °.

Yield: 4,0 g (91%),

Anal.: Calcd.: $C_{29}H_{36}N_2$ C 79,05 H 8,23 N 12,72 Found.: C 78,99 H 8,36 N 12,50.

Methyl-(1,1'-bispiperidinomethyl)-3,3'-diindolylmethane (XXII)

2,66 g of IX (0,01 mole) prepared according to KAMAL [14] from indol with acetaldehyde, M. p.: 164—165 °C (1,7 g of piperidine (0,02 mole) and 1,6 ml of 38% formaldehyde (0,02 mole) were heated in 15 ml ethanol under refluxing for 35 min. During this time 5 ml of distilled water were added dropwise to the reaction mixture. On standing the product crystallized within 2—3 hours.

M. p.: 137 °.

Yield: 2,8 g (61,5%).

Anal.: Calcd.: $C_{30}H_{28}N_2$ C 79,25 H 8,40 N 12,32 Found C 78,90 H 8,36 N 12,10.

Table II

Compound	Summary form	M. w.	Mp.	Anal. Calcd %			Found %			Yield %	Recr.
				C	H	N	C	H	N		
VII	$C_{17}H_{14}N_2$	246,32	170	–	–	–	–	–	–	95	*n*-propanol
XI	$C_{17}H_{12}N_2Cl_2$	315.21	181	64,78	3,84	8,89	65,03	4,04	9,08	88	benzol
XII	$C_{17}H_{12}N_2Cl_2$	315,21	187—188	64,78	3,84	8,89	65,04	3,98	8,72	85	benzol-hexán
XIII	$C_{17}H_{12}N_2Br_2$	404,13	171—172	50,53	2,99	6,94	51,26	3,31	7,39	85	benzol-hexán
XIV	$C_{17}H_{12}N_2Br_2$	404,13	180—181	50,53	2,99	6,94	49,72	2,92	6,60	91	benzol
XV	$C_{17}H_{12}N_2Br_2$	404,13	215— 16	50,53	2,99	6,94	50,47	2,90	7,24	75	benzol-hexán
XVI	$C_{17}H_{12}N_2J_2$	498,12	167—168	40,95	2,43	5,62	41,30	2,42	5,60	80	benzol-hexán
XVII	$C_{19}H_{20}N_2$	276,39	157	82,60	7,29	10,14	82,24	7,42	10,2	92	benzol-c-hexán
XVIII	$C_{17}H_{12}N_4O_2$	336,32	284	60,71	3,60	16,66	60,20	3,45	16,09	96	dioxán

Table III

Compound	Summary form	M. w.	Mp.	Anal. Calcd %			Found %			Yield %
				C	H	N	C	H	N	
XIX	$C_{29}H_{36}N_4$	440,65	140—141	79,05	8,23	12,72	78,99	8,36	12,50	91
XXIV	$C_{29}H_{34}N_4Cl_2$	509,54	135—136	68,36	6,73	11,00	67,83	6,45	11,14	91
XXV	$C_{29}H_{34}N_4Cl_2$	509,504	139—140	68,36	6,73	11,00	67,75	6,80	10,95	88
XXVI	$C_{29}H_{34}N_4Br_2$	598,46	156	58,20	5,73	9,36	57,47	5,81	9,00	80
XXVII	$C_{29}H_{34}N_4Br_2$	598,46	132	58,20	5,73	9,36	57,75	5,75	9,30	79
XXVIII	$C_{29}H_{34}N_4Br_2$	598,46	195—196	58,20	5,73	9,36	57,2	5,92	9,11	90
XXIX	$C_{29}H_{34}N_4J_2$	692,44	139—140	56,30	4,95	8,09	51,05	5,13	7,87	77
XXX	$C_{31}H_{40}N_4$	468,69	143—144	79,44	8,60	11,96	79,76	8,97	12,15	85
XXXI	$C_{29}H_{34}N_5O_4$	530,64	179—180	65,75	6,22	15,85	65,73	6,52	15,72	95

Dimethyl-(1,1'-bispiperidinomethyl)-3,3'-diindolylmethane (XXI)

2,74 g of VIII (0,01 mole) prepared according to KELLER [22] from indol with acetone, M. p. 168 °C (1,7 g piperidine (0,02 mole) and 1,6 ml of 38% formaldehyde (0,02 mole) were prepared similarly as in the former experiment (XXIV).

M. p.: 120,5 °.

Yield: 3,6 g (78%).

Anal.: Calcd.: $C_{31}H_{40}N_2$ C 79,40 H 8,60 N 11,94 Found: C 78,95 H 8,81 N 12.18.

Propyl-(1,1'-bispiperidinomethyl)-3,3'-diindolylmethane (XXIII)

2,88 g of X (0,01 mole) (prepared according to KAMAL [14] from indol with butyraldehyde, M. p.: 171 °) at the same mole ratio and under similar conditions as used at XXIV. It was recrystallized from ethanol-petrolether mixture (2:3).

M. p.: 114—115 °.

Yield: 3,1 g (64,5%).

Anal.: Calc.: $C_{32}H_{42}N_2$ C 79,74 H 8,77 N 11,60 Found C 80,10 H 8,43 N 11,35.

General Description of Preparation of Substituted Diindolylmethane (Compounds of Fig. 4):

0,01 mole of substituted indol (Table I) was dissolved at 70—80 °C in the mixture of 150 ml of water and 40 ml of ethanol under constant stirring. After complete dissolving, 1,9 ml of 1 N sulphuric acid and 0,005 mole of formaldehyde solution were added to the reaction mixture. Heating was carried out for about 6—8 hours in nitrogen atmosphere. During this time the substituted diindolylmethane formed separated from the solution. After cooling it was filtered, washed with distilled water, dried in nitrogen atmosphere. (All the other data are to be seen in Table 2).

General Description of Preparation of Bis-Mannich Bases

0,01 mole diindolylmethane derivative (Table 2) was dissolved in 15—25 ml of ethanol, then 0,02 mole of piperidine and 0,02 mole of formaldehyde solution were added. The reaction mixture was heated for 15—25 min under refluxing. After a period of standing for 2—8 hours the product crystallized. It was filtered and recrystallized from ethanol (see Table 3).

Of these compounds XIX and XX have strong tranquilizing properties [30] Substituting the diindolylmethane skeleton in any position results in decreasing or complete ceasing of this effect.

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СИНТЕЗ НОВЫХ ПРОИЗВОДНЫХ ДИИНДОЛИЛМЕТАНА ВЛИЯЮЩИХ НА ЦЕНТРАЛЬНЫЙ НЕРВНЫЙ МОЗГ. VI

Ш. Фельдеак, Й. Цомбош, Б. Маткович и Й. Порсас

Авторами приготовились несколько производных и бис- *Манних* баз дииндолилметана из индола при помощи оксо-соединений и из 4-, 5- и 6-замещенных индолов при помощи формальдегида.

Механизм образования дииндолилметана и реакции *Манниха* изучался тонкослойной хроматографией.